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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/663,452	09/16/2003	Kenneth W. Dobie	ISIS0044-101/RTS-0378.C1	2696

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ISIS PHARMACEUTICALS INC
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EXAMINER

ASHEN, JON BENJAMIN

ART UNIT	PAPER NUMBER
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1635

DATE MAILED: 08/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/663,452

Applicant(s)

DOBIE, KENNETH W.

Examiner

Jon B. Ashen

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 2 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-24 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☐ Claim(s) ____ is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☒ Claim(s) 1-24 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date ____. | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:
 - I. Claims 1-12 and 14-24, drawn to an antisense compound 8 to 80 nucleobases in length comprising at least 80% sequence complementarity to a nucleic acid molecule encoding beta-site APP-cleaving enzyme 2 (SEQ ID NO: 4), wherein said compound comprises a SEQ ID NO: as listed in claim 19 or 20 and/or specifically hybridizes to a portion of SEQ ID NO: 4 that is identified in claim 1, 14 or 21 or that that specifically hybridizes to the 5' untranslated region, the start codon region, or the 3' untranslated region as required in claim 14 and dependent claims 15-16 and 18, classified in class 536, subclass 24.1. (This group is further restricted below)
 - II. Claim 13, drawn to a method of inhibiting the expression of beta site APP-cleaving enzyme 2 in cells or tissues using the antisense compound of claim 1, classified in class 5114, subclass 44.

The inventions are distinct, each from the other because of the following reasons:

2. Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process

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for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). Invention I is drawn to an antisense compound 8 to 80 nucleobases in length comprising at least 80% sequence complementarity to a nucleic acid molecule encoding beta-site APP-cleaving enzyme 2 (SEQ ID NO: 4). Invention II is drawn to a method of inhibiting the expression of beta site APP-cleaving enzyme 2 in cells or tissues using the antisense compound of claim 1. In the instant case the product as claimed can be used in a materially different process of using that product, such as a hybridization assay to determine cell or tissue specific expression of beta site APP-cleaving enzyme 2, for example.

Furthermore, searching Inventions I and II together would impose a serious and undue search burden. In the instant case, a prior art search of the method of Invention II would not be coextensive with a prior art search of the compound of Invention I. Search of each of these inventions would require different key word searches of the compound and of the distinctive steps required by the method using different patent and non-patent literature databases. The different searches would then require subsequent in-depth analysis of the unrelated prior art literature, placing a serious and undue burden on the Office in terms of both search and examination. As such, it would be burdensome to perform examination of Inventions I and II together.

3. Claims 1 and 21 link(s) inventions in Group I (see below) that are each individual SEQ ID NOs: listed in claims 19 and/or 20 that target the specified region of SEQ ID

NO: 4 as set forth in claim 1 and do not target the specified portions of SEQ ID NO: 4 excluded by claim 21. The restriction requirement among the linked inventions is subject to the nonallowance of the linking claim(s), claim 1 and 21. Claim 14 link(s) inventions in Group I that are antisense compounds that specifically hybridize to the 5' untranslated region, the start codon region, the stop codon region, or the 3' untranslated region as listed in claim 14 and dependent claims 15-18 and SEQ ID NO: 88 as listed in claim 19). The restriction requirement among the linked inventions is subject to the nonallowance of the linking claim(s), claim 14. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

4. Pursuant to 35 U.S.C. 121 and 37 C.F.R. 1.141, the antisense sequences listed in claims 19 and 20 and that specifically hybridize to the 5' untranslated region, the start codon region, or the 3' untranslated region as required in claim 14 and dependent

claims 15-16 and 18, are subject to restriction. The Commissioner has partially waived the requirements of 37 C.F.R. 1.141 and will permit a reasonable number of such nucleotide sequences to be claimed in a single application. Under this policy, up to 10 of independent and distinct nucleotide sequences will be examined in a single application. (see MPEP 803.04 and 2434)

Claims 19 and 20 are subject to an additional restriction since it each is not considered to be a proper genus/Markush. See MPEP 803.02 - PRACTICE RE MARKUSH-TYPE CLAIMS - If the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all the members of the Markush group in the claim on the merits, even though they are directed to independent and distinct inventions. In such a case, the examiner will not follow the procedure described below and will not require restriction. Since the decisions in *In re Weber*, 580 F.2d 455, 198 USPQ 328 (CCPA 1978) and *In re Haas*, 580 F.2d 461, 198 USPQ 334 (CCPA 1978), it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention. In *re Harnish*, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and *Ex parte Hozumi*, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility.

Claims 19 and 20 specifically claim antisense sequences as listed, which are targeted to and modulate the expression of beta-site APP-cleaving enzyme 2 (SEQ ID

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NO: 4). Although the antisense sequences claimed each target and modulate expression of beta-site APP-cleaving enzyme 2 (SEQ ID NO: 4), the instant antisense sequences are considered to be unrelated, since each antisense sequence claimed is structurally and functionally independent and distinct for the following reasons: each antisense sequence has a unique nucleotide sequence, each antisense sequence targets a different and specific region of a beta-site APP-cleaving enzyme 2 (SEQ ID NO: 4), and absent evidence to the contrary, each antisense, upon binding to a beta-site APP-cleaving enzyme 2 (SEQ ID NO: 4) nucleic acid, is expected to functionally modulate (increase or decrease) the expression of beta-site APP-cleaving enzyme 2 (SEQ ID NO: 4) to varying degrees. As such the Markush/genus of antisense sequences in claims 19 and 20 are not considered to constitute a proper genus, and are therefore subject to restriction.

Furthermore, a search of more than one (1) of the antisense sequences claimed in claims 14, 19 and 20 presents an undue burden on the Patent and Trademark Office due to the complex nature of the search and corresponding examination of more than one (1) of the claimed antisense sequences. MPEP 808.02 states in part: Where the related inventions as claimed are shown to be distinct under the criteria of MPEP 806.05(C) - 806.05(i), the examiner, in order to establish reasons for insisting upon restriction, must shown by appropriate explanation one of the following:

(C) A different field of search: Where it is necessary to search for one of the distinct subjects in places where no pertinent art to the other subject exists, a different field of search is shown, even though the two are classified together.

It is noted that a search of the available sequence databases produces a listing of references disclosing the sequence most similar to the query sequence. This is the "place" where the examiner searches for prior art. The prior art relating to another query sequence will not be found in this "place"- a different listing of references must be generated and searched by the examiner. Thus a different search is shown, and restriction is proper.

In view of the foregoing, one (1) antisense sequence is considered to be a reasonable number of sequences for examination. Accordingly, applicant is required to elect one (1) sequence from claims 19 and 20 that corresponds with a target region as claimed and listed in claim 1 or 21 or to elect an invention that is an antisense compound that is not one of the SEQ ID NOs: listed above that specifically hybridizes to the distinct nucleotide sequences of SEQ ID NO: 4 that are the 5' untranslated region, the start codon region, or the 3' untranslated region as required in claim 14 and dependent claims 15-16 and 18. Note that this is not a species election.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon B. Ashen whose telephone number is 571-272-2913. The examiner can normally be reached on 7:30 am - 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Jba

Jane Zane
TC1600